

# MODERN INSULIN AND INSULIN THERAPY IN DIABETES MELLITUS

by

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## INTRODUCTION

INSULIN is a complex polypeptide hormone, prepared in crystalline form from the pancreas of suitable animals and available for the parenteral administration to patients whose endogenous supply of insulin is insufficient to maintain normal carbohydrate metabolism. About one-third of diabetic patients need insulin, and a great variety of commercial preparations, some newly introduced on the market, are available for their treatment.

## PREPARATIONS OF INSULIN\*

Much of the insulin used in Britain has, until recently, been derived from ox pancreas, whereas pork insulins predominate in Europe. All standard insulin preparations are impure and stimulate the production of antibodies. Pork insulins are less antigenic than beef since the structure of the former resembles the human form more closely than the latter. Newer highly purified pork insulins have been subjected to further re-crystallization and gel-filtration, and only rarely provoke antibody formation. Purified beef insulin preparations from which immunogenic proinsulin has been largely removed (less than 20 ppm) have just been introduced.

Preparations of insulin can be divided into three groups, depending on their length and speed of action, namely, short-acting with rapid onset, intermediate and long-acting. Except for the short-acting soluble insulins, all other types have been modified to delay absorption and increase the duration of action. This is achieved by the addition of zinc or a protein, or both, in the presence of a suitable buffer.

## SHORT-ACTING INSULINS

*Soluble insulin* (insulin injection BP, unmodified or regular, SI) is a clear aqueous solution of beef insulin with a pH of 3.0 to 3.5. SI acts quickly and more intensely than the modified insulins.

*Neutral soluble insulin* (Nuso, neutral injection BP) is a crystalline insulin derived from beef or pork pancreas with a pH of 6.6 to 7.7 *Actrapid MC* (Novo) and *Insulin Leo Neutral* (Nordisk) are neutral highly purified pork insulin preparations. *Semilente* is a neutral suspension of zinc insulin (IZS) in amorphous form prepared from beef or pork insulin, and *Semitard MC* (Novo) is the equivalent in highly purified pork insulin. *Semilente* (Novo) is proinsulin free (PIF) pork insulin.

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\* A detailed list of the preparations of insulin in current use may be obtained from Dr. Marie Maguire, Drug Information Centre, The Pharmacy, Royal Victoria Hospital, Belfast BT12 6BA.

Because of their fast action, the soluble insulins are the preparations of choice for the treatment of diabetic ketosis and coma and for surgical emergencies. When injected subcutaneously their action lasts from  $\frac{1}{2}$  to 8 hours, with a peak between  $1\frac{1}{2}$  and 4 hours. Neutral soluble insulin and the highly purified pork preparations have a slightly faster rate of action than SI, probably because the pH of the latter has to rise before it becomes biologically active and possibly to a lack of insulin binding in the plasma by the purified insulins. The action of Semilente and Semitard lasts between  $1\frac{1}{2}$  and 14 hours and is at its peak between 4 and 9 hours.

### INTERMEDIATE INSULINS

*Isothane insulin BP (NPH)* is a suspension of beef crystalline insulin, protamine and zinc, buffered with phosphate (pH 7.1 to 7.4). *Leo Retard* is a neutral, highly purified micro-crystalline pork isophane preparation. Both SI and Leo Neutral can be mixed with their appropriate isophane preparation (beef for the former and pork for the latter) without causing loss of action of either due to precipitation of free zinc. *Mixtard (Leo)* is a preparation containing a mixture of Leo Neutral (30 per cent) with Leo Retard (70 per cent). *Globin zinc insulin BP* is an acidic solution of beef insulin, modified by the addition of a suitable globin and zinc (pH 3.0 to 3.5). *Biphasic insulin BP* is a neutral mixture of beef insulin crystals (75 per cent) suspended in a solution of pork insulin. *Rapitard (Novo)* consists of a mixture of PIF beef insulin crystals in a solution of highly purified pork insulin. *Lente insulin (IZS)* is a neutral mixture of seven parts of crystalline zinc suspension (Ultralente) and three parts of amorphous suspension (Semilente). *Lentard (Novo)* is a PIF beef preparation of Lente. *Monotard MC (Novo)* is the highly purified pork equivalent of Lente.

The action of Isothane, Leo Retard, Globin Zinc and Rapitard commences at  $1\frac{1}{2}$  hours and continues for 24 hours, with maximum effect between 4 and 12 hours. There are minor variations between the different preparations. Lente, Lentard and Monotard have a slightly slower onset of action ( $2\frac{1}{2}$  hours) and last fully 24 hours, with the peak response between 6 and 14 hours.

### LONG-ACTING INSULINS

*Protamine zinc insulin (PZI)* is a combination of beef or pork insulin with added protamine and zinc, phosphate buffered to a pH of 6.9 to 7.3. *Ultralente insulin (IZS)* is a neutral suspension of crystalline beef insulin. *Ultratard (Novo)* is a PIF preparation of Ultralente. Onset of action of these preparations is delayed for 4 hours and continues for 30 or more hours, depending on the dose, with the maximum effect between 10 and 18 hours.

*Highly purified pork insulins* were introduced for clinical use in Britain in 1975. These insulins differ from standard beef or pork insulin and patients accustomed to ordinary preparations may develop hypoglycaemia if they are changed to an equivalent dose of a highly purified insulin because of lack of resistance. Highly purified pork insulins do not give rise to antibodies in previously untreated diabetics, or, if they do, these are of very low titre, and there may be a modest, sometimes substantial drop (immediate or delayed) in insulin requirement on

changing to a purified preparation. A 20 per cent reduction in dose is advisable when substituting one of these preparations and further adjustments, either up or down, should be carefully supervised. Cutaneous sensitivity reactions and lipotrophy have been largely abolished, and remission periods are said to last longer.

*Purified beef insulins*, from which immunogenic proinsulin substances have been largely reduced (less than 20 ppm) became available for clinical use early in 1976. Patients currently maintained on Novo Lente, Ultralente and Rapitard can be changed to the equivalent PIF preparation without readjustment of the dose.

## INSULIN STRENGTHS

Insulin is standardised in International Units to ensure that the dose remains constant. With few exceptions, insulin is available in 40 and 80 unit strengths. Recently, preparations containing 100 units per ml (U-100) have been introduced in the USA and Canada with the object of phasing out U-40 and U-80. However, U-40 and U-80 preparations are still listed in the USP (18th ed., 1975).

## INDICATIONS FOR INSULIN THERAPY

Insulin is required for the treatment of diabetic ketosis and for all diabetics who cannot be kept in good health without it. It should be avoided in the obese, unless it is required temporarily to treat ketosis, to cover infections, surgical operations and to relieve diabetic vulvitis. Insulin is usually indicated for patients with active retinopathy, neuropathy or nephropathy, for young diabetics with cataracts and during pregnancy. Obese patients with complications, however, gain little from the addition of insulin if the blood glucose can be kept at normal levels without it.

## METHODS OF USING INSULIN

The range of insulin preparations is such that it should be possible to achieve excellent control in most stable diabetics and good control in the majority of brittle diabetics. The selection of a suitable regime depends on the patient, the nature of the diabetes and the experience of the physician.

### TWICE DAILY REGIMES

Soluble insulin, Nuso, Actrapid MC and Leo Neutral, injected 10 to 20 minutes before the morning and evening meals, are used for the initial stabilisation of new diabetics and for the treatment of diabetic ketosis and other complications. It is probably advisable now to start new diabetics on a highly purified pork or beef preparation. The disadvantage of extra cost (approximately the same to more than twice as expensive) is balanced by smaller doses and freedom from allergic side effects.

When employed twice daily they usually provide control of the plasma glucose level equal or superior to most single dose injection regimes. The chief disadvantage is the short duration so that patients with severe diabetes frequently show *hyperglycaemia* for some hours before the next injection of insulin is due. This fluctuation makes stabilisation difficult and *hypoglycaemia* results if the dose of

SI is increased in an attempt to control the hyperglycaemia peak, but it can often be overcome by combining Isophane with one or both doses of SI, allowing 3 or 4 units of Isophane for each unit of SI. This combination prolongs the action of the insulin and allows a reduction in the dose of SI and the danger of hypoglycaemia. A similar effect can be achieved with a combination of Actrapid MC or Semitard MC and Montard MC, by a mixture of Semilente and Lente insulin or Leo Neutral and Retard. The combination of a quick and intermediate-acting insulin twice daily provides the most effective control for patients with severe or brittle diabetes.

#### SINGLE DOSE REGIMES

Any of the intermediate insulins (Isophane, Leo Retard, Lente or Monotard MC) may provide acceptable control for 18 to 24 hours after a morning injection. The method is satisfactory for mild diabetics (approximately one-third of those requiring insulin). These preparations frequently provide good control in the afternoon and evening without affecting appreciably the morning hyperglycaemia. The administration of a short-acting insulin (SI, Leo Neutral, Actrapid MC or Semitard MC) with the morning dose or the use of Mixtard or Rapitard may avoid this difficulty. Sometimes the converse is seen, when control in the morning and afternoon is good, but hyperglycaemia returns in the evening and persists overnight. Such a pattern requires the addition of a second dose of a quick-acting or intermediate insulin before the evening meal. Alternatively, the effect of a morning dose of Lente or Lentard can be protracted by the addition of some Ultralente or Ultratard. Patients needing more than 60 units per day can rarely be controlled satisfactorily on a single morning injection of an intermediate or long-acting preparation. In general, single dose regimes are unsuitable for children and adolescents, pregnant diabetics, for patients with diabetic complications, for those with infections or ketosis and for those undergoing surgical operations.

#### INSULIN MIXTURES

Soluble insulin and Isophane can be injected together in the same syringe without their individual actions being altered significantly. Various combinations of the insulin zinc suspensions and highly purified insulins may be tried to obtain relatively constant plasma glucose levels throughout the 24 hours. Actrapid MC, Leo Neutral, Semilente or Semitard MC may be added to Lente to increase the speed of action earlier in the day, or Ultralente may be added to Semilente or Lente, or Monotard MC to Semitard MC, to provide a protracted effect. It must be noted that the non-antigenic properties of highly purified insulins are destroyed if they are mixed with insulins which are not of highly purified pork origin. The admixture of SI and Lente is not recommended, since the two preparations differ in pH; Actrapid MC or Nuso are preferred.

#### ADVERSE REACTIONS TO INSULIN

These may be local or general. A *local stinging* or a *tender indurated swelling* at the site of injection is seen in about 40 per cent of patients seven to ten days after insulin treatment has been started with the older preparations. The cutaneous

swellings may persist for a few weeks and subside spontaneously. Unless severe, the patient should be reassured and treatment need not be interrupted. Should they persist it is advisable to change to a highly purified preparation. *True insulin allergy* is rare and is similar to the allergy caused by other antigens. Most insulin allergies occur with modified insulins derived from the more antigenic beef preparations, so that it may be necessary to rely on a highly purified neutral pork soluble insulin. *Lipoatrophy* (insulin atrophy) is the most frequent long-term adverse reaction to standard insulins but it is rarely seen with the new purified preparations. The cause is unknown although antigenic impurities of insulin may be a factor and, until recently, there was no reliable cure. Recently it has been shown that the injection of neutral soluble insulin into the affected area or changing to a highly purified preparation is beneficial. *Lipohypertrophy* is rare and consists of a large subcutaneous mass of fatty tissue which develops at the site of repeated injections of insulin. The swelling may disappear when insulin is no longer injected, but large tumours may require surgical removal.

### CONCLUSIONS

The variety of current insulin preparations is so extensive that the successful treatment of all insulin-dependent diabetics should be possible whether they are stable or not. Unfortunately, the range is so wide that few general physicians can gain expert knowledge of all varieties. However, the soluble insulins, Isophane, the highly purified preparations and the insulin zinc suspensions cover the needs of most patients. Special combinations, arrived at by trial and error, are usually necessary for the minority with brittle diabetes.

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